REMARKS

I. INTRODUCTION

Receipt of the Office Action of June 6, 2002 is acknowledged. Claims 1, 3, 4, 7, 8, 10, 11, 13, 16, 20, 23, 26, 30, 33, 36, 76, 78 and 80 have been amended to more particularly point out and distinctly claim the subject matter Applicants regard as their invention. Claims 2, 6, 9, 12, 35, 37 and 49 have been canceled without prejudice or disclaimer. The cancellation of claims does not constitute acquiescence to the propriety of any rejection or objection set forth by the Examiner. New claims 85-87 have been added and are based on claim 49. The amendments to the claims are supported by specification, see, e.g., page 28, line 30-page 29, line 2.

After amending the claims as set forth above, claims 1, 3-5, 7-8, 10-11, 13-34, 36, 38-48 and 50-87 are now pending in this application.

II. THE OFFICE ACTION

A. Election/Restriction

The Examiner has stated that the original restriction requirement has been withdrawn, but that the election of species requirement is maintained.

B. Specification

The Examiner stated that the lengthy specification has not been checked for all possible errors. Applicants are not aware of any errors and request that the Examiner point any errors that may have been determined during the examination process.

C. Rejections based on 35 U.S.C. § 112, first paragraph

The Examiner has rejected claims 78 and 80 under 35 U.S.C, § 112, first paragraph as allegedly lacking enablement for "preventing" a protein kinase related disorder." Applicants respectfully traverse. Without acquiescing to the position of the Examiner, claims 78 and 80 have been amended to delete the recitation of "preventing" from the claims. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

D. Rejections based on 35 U.S.C. § 102(b)

The Examiner has rejected claim 1 under 35 U.S.C. § 102(b) as allegedly anticipated by Tang (U.S. Patent No. 5,792,783). Applicants respectfully traverse.

It is the Examiner's position that the language of "ionizable substituted indolinone" of claim 1 is anticipated by Tang (U.S. Patent No. 5,792,783). Without acquiescing to the position of the Examiner, claim 1 now incorporates the indolinone chemical structure of claim 2, along with other amendments, to more particularly point out the subject matter that Applicants regard as their invention. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

E. Rejections based on 35 U.S.C. § 103

The Examiner has rejected claims 1-84 under 35 U.S.C. § 103 as allegedly unpatentable over Tang (U.S. Patent No. 5,792,783, hereafter, "Tang '783"). Applicants respectfully traverse.

At the outset, it is unclear whether the Examiner has extended the search beyond the elected species because the Examiner states in the "Election/Restriction" section of the Office Action that the election of species is maintained and that the elected species is rendered obvious by Tang '783. Clarification is requested.

It is respectfully submitted that Tang '783 cannot render obvious the claimed invention. The Examiner has rejected the claims over Tang '783 by asserting that the present claims are a more limited genus as compared to the claims of Tang '783. This rejection does not meet the requirements of a *prima facie* case of obviousness for the following reasons.

For a proper *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art references (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the

reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure. See MPEP 2142.

In this regard, the Examiner has failed to follow the guidelines for examination of chemical genus-species as published in the Federal Register on September 3, 1998, at 980826. These guidelines are set forth at MPEP § 2144.08.

MPEP § 2144.08 also provides that the patentability of a claim to a specific compound or subgenus embraced by a prior art genus should be analyzed no differently than any other claim for purposes of 35 U.S.C. § 103. "The section 103 requirement of unobviousness is no different in chemical cases than with respect to other categories of patentable inventions." *In re Papesch*, 315 F.2d 381, 385, 137 USPQ 43, 47 (CCPA 1963).

The PTO has explicitly stated that the type of rejection set forth by the Examiner does not constitute a proper *prima facie* obviousness case. MPEP § 2144.08 states: "[t]he fact that a claimed species or subgenus is encompassed by a prior art genus is not sufficient by itself to establish a *prima facie* case of obviousness. *See In re Baird*, 16 F.3d 380, 382, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994) ('The fact that a claimed compound may be encompassed by a disclosed generic formula does not by itself render that compound obvious.')." Thus, without more, Tang '783 cannot render obvious claims directed to a formulation comprising an ionizable substituted indolinone compound since Tang '783 fails to teach all the claim limitations of the presently claimed invention.

Moreover, the elected compound requires that R^8 and R^{10} are methyl and that R^9 is a propionic acid moiety. Furthermore, there is no teaching or suggest in Tang '783 of the "(alk_1)-Z" moiety on the pyrrole bonded to the indolinone ring which is recited in original claim 2 (". . . providing, however that at least one of R^8, R^9 or R^{10} is a group having the formula –(alk_1)-Z") and is now recited in all the pending claims. Therefore, contrary to the Examiner's assessment, the elected species is not rendered obvious by Tang '783. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

It is requested that the Examiner follow the procedure of MPEP 803.02 for further search and examination of the entire claimed invention.

III. CONCLUSION

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

Date Dec. 6, 2002 By Mary C Till

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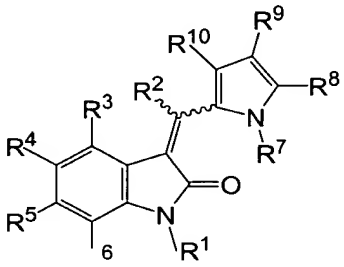
MARKED UP VERSION SHOWING CHANGES MADE

1. (Amended) A formulation suitable for parenteral or oral administration, said formulation comprising an ionizable substituted indolinone of Formula (I);



(I)

wherein

R^1 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, hydroxy, alkoxy, C-carboxy, O-carboxy, acetyl, C-amido, C-thioamido, sulfonyl and trihalomethanesulfonyl;

R^2 is selected from the group consisting of hydrogen, halo, alkyl, cycloalkyl, aryl, heteroaryl and heteroalicyclic;

R^3, R^4, R^5 and R^6 are independently selected from the group consisting of hydrogen, alkyl, trihaloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, mercapto, alkylthio, arylthio, sulfinyl, sulfonyl, S-sulfonamido, N-sulfonamido, trihalomethane-sulfonamido, carbonyl, C-carboxy, O-carboxy, C-amido, N-amido, cyano, nitro, halo, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, amino and $-NR^{11}R^{12}$;

R^{11} and R^{12} are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, carbonyl, acetyl, sulfonyl, trifluoromethanesulfonyl and, combined, a five- or six-member heteroalicyclic ring;

R^3 and R^4, R^4 and R^5, or R^5 and R^6 may combine to form a six-member aryl ring, a methylenedioxy group or an ethylenedioxy group;

R^7 is selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, carbonyl, acetyl, C-amido, C-thioamido, amidino, C-carboxy, O-carboxy, sulfonyl and trihalomethane-sulfonyl;

R^9 is -(alk_1)Z, wherein Alk_1 is selected from the group consisting of alkyl, alkenyl or alkynyl, and Z is a polar group;

R^8 and R^9 are independently selected from hydrogen and unsubstituted lower alkyl, one or more polyoxyhydrocarbyl compounds and a pharmaceutically acceptable carrier therefor, wherein said ionizable substituted indolinone is solubilized by combining said indolinone with a molar equivalent of a base solution or an acid solution**[comprises at least one or more hydrocarbon chains substituted with at least one polar group]**.

3. (Amended) The formulation of claim **[2]** 1, wherein said ionizable substituted indolinone is 3-[2,4-dimethyl-5-(2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-1H-pyrrol-3-yl]-propionic acid, or a pharmaceutically acceptable salt, prodrug, derivative, or analog thereof.

4. (Amended) The formulation of claim **[2]** 1, wherein said formulation is suitable for parenteral administration.

7. (Amended) The formulation of claim **[6]** 1, wherein each of said one or more polyoxyhydrocarbyl compounds is independently selected from the group consisting of water soluble carbohydrates, water soluble carbohydrate derivatives, water soluble polypeptides, water soluble polymers, water soluble mixed oxyalkylene polymers, the polymeric forms of ethylene glycol, and combinations thereof.

8. (Amended) The formulation of claim **[6]** 1, wherein each of said one or more polyoxyhydrocarbyl compounds is independently selected from the group consisting of polyethylene glycol 300, polyethylene glycol 400, propyleneglycol, glycerin, and combinations thereof.

10. (Amended) The formulation of claim **[9]** 1, wherein said base solution is selected from the group consisting of sodium hydroxide, ammonium hydroxide, triethylamine, ethylenediamine, N-methyl-D-glucamine, choline, and triethanolamine.

11. (Amended) The formulation of claim **[9]** 1, wherein said acid solution is selected from the group consisting of hydrochloric acid, sulfuric acid, formic acid, lactic acid, malic acid, succinic acid, acetic acid, methane sulfonic acid, benzene sulfonic acid, and phosphoric acid.

13. (Amended) The formulation of claim **[6]** 1, wherein said pharmaceutically acceptable carrier further comprises one or more buffers.

16. (Amended) The formulation of claim **[6]** 1, wherein said pharmaceutically acceptable carrier further comprises one or more pharmaceutically acceptable surfactants.

20. (Amended) The formulation of claim **[6]** 1, wherein said pharmaceutically acceptable carrier further comprises one or more pharmaceutically acceptable preservatives.

23. (Amended) The formulation of claim **[6]** 1, wherein said pharmaceutically acceptable carrier further comprises one or more antioxidants.

26. (Amended) The formulation of claim **[6]** 1, wherein said pharmaceutically acceptable carrier further comprises one or more pharmaceutically acceptable alcohols.

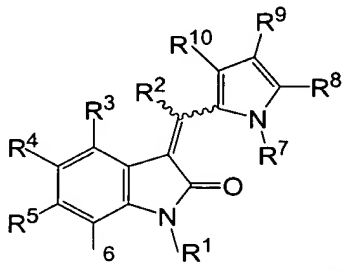
30. (Amended) The formulation of claim **[6]** 1, wherein said pharmaceutically acceptable carrier further comprises one or more pharmaceutically acceptable oils.

33. (Amended) The formulation of claim **[2]** 1, wherein said formulation is suitable for oral administration.

36. (Amended) The formulation of claim **[35]** 33, wherein each of said one or more polyoxyhydrocarbyl compounds is independently selected from the group consisting of water soluble carbohydrates, water soluble carbohydrate derivatives, water soluble

polypeptides, water soluble polymers, water soluble mixed oxyalkylene polymers, and the polymeric forms of ethylene glycol.

76. (Amended) A method of making a formulation suitable for oral administration comprising admixing an ionizable substituted indolinone of Formula (I);



(I)

wherein

R^1 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, hydroxy, alkoxy, C-carboxy, O-carboxy, acetyl, C-amido, C-thioamido, sulfonyl and trihalomethanesulfonyl;

R^2 is selected from the group consisting of hydrogen, halo, alkyl, cycloalkyl, aryl, heteroaryl and heteroalicyclic;

R^3, R^4, R^5 and R^6 are independently selected from the group consisting of hydrogen, alkyl, trihaloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, mercapto, alkylthio, arylthio, sulfinyl, sulfonyl, S-sulfonamido, N-sulfonamido, trihalomethane-sulfonamido, carbonyl, C-carboxy, O-carboxy, C-amido, N-amido, cyano, nitro, halo, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, amino and $-NR^{11}R^{12}$;

R^{11} and R^{12} are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, carbonyl, acetyl, sulfonyl, trifluoromethanesulfonyl and, combined, a five- or six-member heteroalicyclic ring;

R^3 and R^4, R^4 and R^5, or R^5 and R^6 may combine to form a six-member aryl ring, a methylenedioxy group or an ethylenedioxy group;

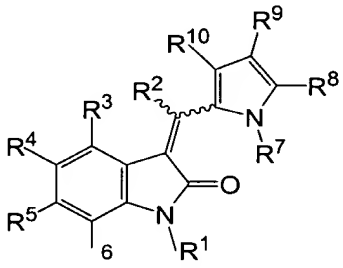
R^7 is selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, carbonyl, acetyl, C-amido, C-thioamido, amidino, C-carboxy, O-carboxy, sulfonyl and trihalomethane-sulfonyl;

R^9 is -(alk_1)Z, wherein Alk_1 is selected from the group consisting of alkyl, alkenyl or alkynyl, and Z is a polar group;

R^8 and R^9 are independently selected from hydrogen and unsubstituted lower alkyl, one or more pharmaceutically acceptable surfactants, and one or more pharmaceutically acceptable oils.

78. (Amended) A method of **[preventing or]** treating a protein kinase related disorder in a patient in need of treatment comprising:

a. diluting a parenteral formulation into a pharmaceutically acceptable solution, said parenteral formulation comprising an ionizable substituted indolinone of Formula (I);



(I)

wherein

R^1 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, hydroxy, alkoxy, C-carboxy, O-carboxy, acetyl, C-amido, C-thioamido, sulfonyl and trihalomethanesulfonyl;

R^2 is selected from the group consisting of hydrogen, halo, alkyl, cycloalkyl, aryl, heteroaryl and heteroalicyclic;

R^3, R^4, R^5 and R^6 are independently selected from the group consisting of hydrogen, alkyl, trihaloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, mercapto, alkylthio, arylthio, sulfinyl, sulfonyl, S-sulfonamido, N-sulfonamido, trihalomethane-sulfonamido, carbonyl, C-carboxy, O-carboxy, C-amido, N-amido, cyano, nitro, halo, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, amino and $-NR^{11}R^{12}$;

R^{11} and R^{12} are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, carbonyl, acetyl, sulfonyl, trifluoromethanesulfonyl and, combined, a five- or six-member heteroalicyclic ring;

R^3 and R^4, R^4 and R^5, or R^5 and R^6 may combine to form a six-member aryl ring, a methylenedioxy group or an ethylenedioxy group;

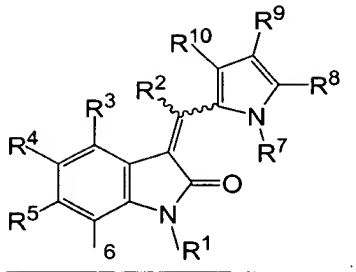
R^7 is selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, carbonyl, acetyl, C-amido, C-thioamido, amidino, C-carboxy, O-carboxy, sulfonyl and trihalomethane-sulfonyl;

R^9 is $-(alk_1)Z$, wherein Alk_1 is selected from the group consisting of alkyl, alkenyl or alkynyl, and Z is a polar group;

R^8 and R^9 are independently selected from hydrogen and unsubstituted lower alkyl, one or more polyoxyhydrocarbyl compounds, and a buffer;

b. parenterally administering said diluted formulation to said patient.

80. (Amended) A method of **[preventing or]** treating a protein kinase related disorder in a patient in need of treatment comprising orally administering to said patient a formulation comprising an ionizable substituted indolinone of Formula (I);



(I)

wherein

R^1 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, hydroxy, alkoxy, C-carboxy, O-carboxy, acetyl, C-amido, C-thioamido, sulfonyl and trihalomethanesulfonyl;

R^2 is selected from the group consisting of hydrogen, halo, alkyl, cycloalkyl, aryl, heteroaryl and heteroalicyclic;

R^3, R^4, R^5 and R^6 are independently selected from the group consisting of hydrogen, alkyl, trihaloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, mercapto, alkylthio, arylthio, sulfinyl, sulfonyl, S-sulfonamido, N-sulfonamido, trihalomethane-sulfonamido, carbonyl, C-carboxy, O-carboxy, C-amido, N-amido, cyano, nitro, halo, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, amino and $-NR^{11}R^{12}$;

R^{11} and R^{12} are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, carbonyl, acetyl, sulfonyl, trifluoromethanesulfonyl and, combined, a five- or six-member heteroalicyclic ring;

R^3 and R^4, R^4 and R^5, or R^5 and R^6 may combine to form a six-member aryl ring, a methylenedioxy group or an ethylenedioxy group;

R^7 is selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, carbonyl, acetyl, C-amido, C-thioamido, amidino, C-carboxy, O-carboxy, sulfonyl and trihalomethane-sulfonyl;

R^9 is -(alk_1)Z, wherein Alk_1 is selected from the group consisting of alkyl, alkenyl or alkynyl, and Z is a polar group;

R^8 and R^9 are independently selected from hydrogen and unsubstituted lower alkyl, one or more pharmaceutically acceptable surfactants, and one or more pharmaceutically acceptable oils.